PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001307	09.02.2005	13.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/30, A61K39/395, A61P35/00

Applicant
MICROMET AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001307

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-12 (IA)

because:

☒ the said international application, or the said claims Nos. 1-12 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	15-16
	No:	Claims	1-14,17-22
Industrial applicability (IA)	Yes:	Claims	13-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:
D1: XP008052075, Technology evaluation: ING-1, XOMA, L.L. Lewis, Vol. 5, Nr 4, 433-436, Current Opinion in molecular therapeutics

5.1 Novelty:

Document D1 discloses a human antibody ING-1 against the human EpCAM antigen (see paragraph introduction). The ING-1 plasma half-life by human and intravenously administered shows values between 17 to 40 hours (see paragraph Clinical development, phase I/II), thus necessitating a more frequent dosing schedule (eg weekly)(see page 435, first paragraph). The ING-1 is used as anticancer agent (see introduction part).

None of the cited documents disclose a human Ig binding to EpCAM exhibiting a serum half-life of at least 15 days after administration to a human patient.

The subject-matter of entity claims 13-16 is therefore new (Article 33(2) PCT). Use claims 1-12 and 17-22 are also considered to be new.

5.2 Inventive step:

Document D1 is considered to represent the most relevant state of the art. The

subject-matter of claim 13-16 and formulated in terms of technical features, differs in that the Ig amino-acid sequence of the claimed antibody is different from D1.

The effect of missing technical feature is that the half-life is increased (at least 15 days).

The objective remaining problem to be solved by the present invention may therefore be formulated as to provide an immunoglobulin capable of exhibiting a serum half-life of at least 15 days.

The proposed solution is as disclosed in claim 15, with the two amino-acid sequences.

This solution can be considered as involving an inventive step for the following reasons none of the cited document would encourage the skilled man in the art to design an antibody as described in claim 15.

The solution to this problem proposed in claim 15 of the present application is therefore considered as involving an inventive step (Article 33(3) PCT). Claims 16 is dependent on claim 15 and as such also meets the requirements of the PCT with respect to inventive step. Independent claims 1 and 17 concern the use of the antibody of claim 15. Claims 1 and 17 will be recognized as involving an inventive step as soon as they include all the features of claim 15.

5.3 Claims 1-12 involve compositions or substances in a method of treatment of the human/animal body.
For the assessment of the present claims 1-12 on the question wether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EP, for instance, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

8.1 It is clear from the description on page 13, li 26 that an intravenous administration is essential to the performance of the invention. Since independent claims 1,13 and 17 does not contain this feature they do not meet the requirement following Article 6 PCT that any independent claim must contain all the technical features essential to the invention. This objection is corroborated by D1, page 434, paragraph metabolism, indicating that dependent on the way of administration (intravenous or subcutaneous), the corresponding half-lives are different.

8.2 It is clear from examples of the description that the treatment is foreseen to be administered to a human patient. Independent claims 1 and 13 contain this feature, but not independent claim 17 : even if the human immunoglobulin used binds to the human EpCAM, this is not clear enough that it has to be administered to a human a patient. Since independent claim 17 do not contain this feature it does not meet the requirement following Article 6 PCT that any independent claim must contain all the technical features essential to the invention.

8.3 Independent claim 13 and dependent claim 14 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved : "said immunoglobulin exhibits a serum half-life of at least 15 days ". In this instance, however, such a formulation is not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved. The solution to overcome this objection is to add the features of claim 15 in independent claim, as already suggested in the problem-solution approach. The same applies to independent claims 1 and 17.

8.4 The vague and imprecise statement in the description on page 13, li 14-20 and page 24, li 26-33 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them. This statement should therefore be amended to remove this inconsistency.

8.5 The wording "The prior art documents .... incorporated by reference" page 3, li 17,20,24,27,29 seeks to extend the scope of protection sought in some vague and

indefinite manner.

8.6 Clerical errors:

- page 4, li 23: ING-1
- page 5, li 19: Fc-γ-RIII
- page 12, li 18: "ing" and "img molecule"

8.7 CONCLUSIONS

In the light of the above observations the IPEA would particularly appreciate the reformulation of independent claim 1,13,17 and claims dependent thereon, to include all the essential technical features as outlined above, such that the claims reflect the nature of the present invention and may be deemed to satisfy the requirements of the PCT.